

Parathyroid carcinoma in familial hyperparathyroidism

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SUMMARY Two families with hereditary hyperparathyroidism are described. One member of each family developed a parathyroid carcinoma. In one case this recurred locally and metastasised. This patient showed hyperplasia of one of the three other parathyroid glands. It is possible that the different parathyroid lesions found in familial hyperparathyroidism may be the result of a progression from hyperplasia to formation of benign or malignant tumours. The remaining hyperplastic glands may be suppressed by hypercalcaemia. There was no evidence of multiple endocrine neoplasia in either family. Three members of the first family had ichthyosis and both affected members of the second had tumours of the jaw, one of which was an ossifying fibroma, suggesting a possible association of these conditions with familial hyperparathyroidism.

Familial hyperparathyroidism was first described by Goldman and Smyth in 1936, and many cases have subsequently been reported. More recently, it has been recognised as a component of the multiple endocrine neoplasia (MEN) syndromes, type I (Wermer, 1954) and type II (Steiner *et al.*, 1968). The parathyroid lesions described most often have been chief cell hyperplasia (nodular hyperplasia) and parathyroid adenoma (Wermer, 1954; Cutler *et al.*, 1964; Schachner *et al.*, 1966; Jackson and Boonstra, 1967). Only a few cases of parathyroid carcinoma in familial hyperparathyroidism have been described (Frayha *et al.*, 1972; Mallette *et al.*, 1974; Leborgne *et al.*, 1975). We wish to present two further cases of parathyroid carcinoma occurring in separate families with familial hyperparathyroidism.

Family A (Fig. 1)

CASE A1

The proband was a 33-year-old woman who presented with an 18-month history of lassitude, thirst, polyuria, and weight loss and recent amenorrhoea and bone pains. On examination she was ill and dehydrated. There was generalised muscular weakness and bone tenderness. Corneal, conjunctival, and

tympanic membrane calcification were noted. There was no palpable mass in the neck.

Investigations showed extreme hypercalcaemia: serum calcium 5.55 mmol/l (22.2 mg/100 ml), serum phosphate 1.29 mmol/l (4.0 mg/100 ml), alkaline phosphatase 90 iu/l. Her blood urea was raised (19.2 mmol/l; 114 mg/100 ml) and she had a generalised aminoaciduria. The serum parathyroid hormone (PTH) was grossly increased at 8 ng/ml (normal < 1.0 ng/ml). Radiological examination revealed widespread cortical bone erosions and bilateral nephrocalcinosis. A barium swallow demonstrated displacement of the oesophagus by an extrinsic mass in the left side of the neck.

Surgical exploration revealed a large tumour arising in the left upper parathyroid and invading the thyroid and muscle coat of the oesophagus. The tumour was removed en bloc with the left lobe of the thyroid, part of the oesophageal wall, and a segment of the recurrent laryngeal nerve, which was entrapped in the tumour. Over the next three days the serum calcium fell to normal and the renal tubular abnormalities rapidly regressed.

However, 18 months later the serum PTH had risen to 2.5 ng/ml, and one month after this hypercalcaemia returned (serum calcium 3.20 mmol/l; 12.8 mg/100 ml), suggesting a recurrence of the tumour. It was felt that surgical resection of any locally recurrent tumour offered the only hope of

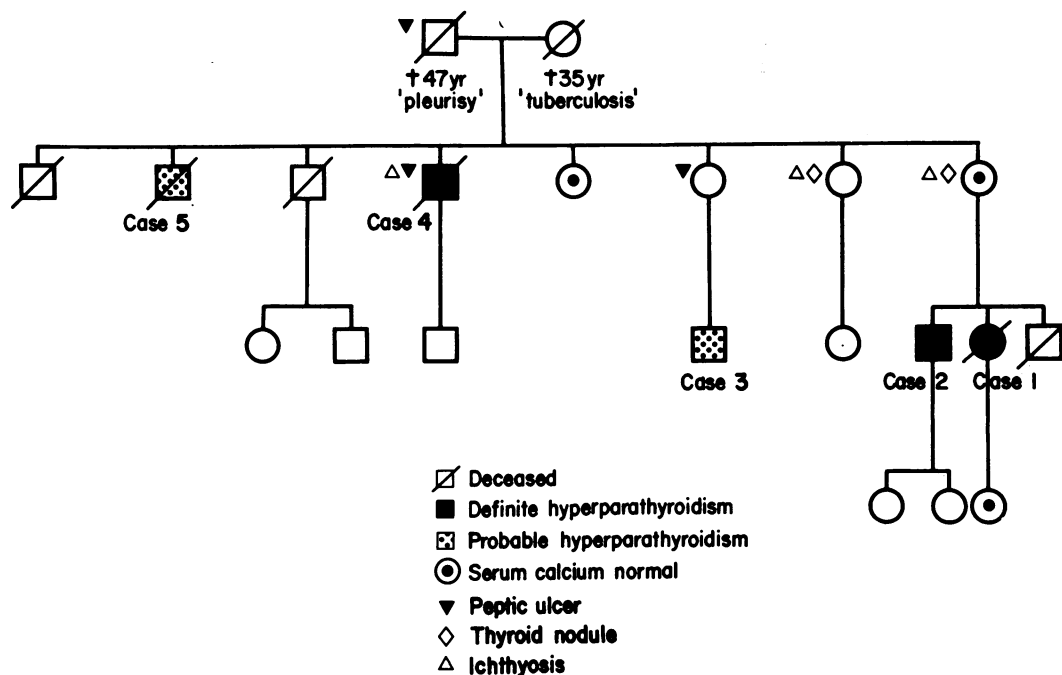


Fig. 1 Family tree of family A.

effective treatment. At the time of operation the serum calcium was 4.70 mmol/l (18.8 mg/100 ml) and the serum PTH was greater than 10 ng/ml.

In view of the oesophageal invasion by the original tumour, an oesophagolaryngectomy was carried out and the remaining lobe of the thyroid was removed. However, the serum calcium remained high and the patient died suddenly nine days after the operation. Permission for a necropsy was refused.

Pathology

The tumour was 3 cm in diameter with a white, lobulated, cut surface (Fig. 2) and an incomplete fibrous capsule. Tumour infiltrated fat, thyroid capsule, and muscle of the oesophageal wall. Numerous blood vessels were permeated by columns of tumour cells and several small nerves were completely engulfed. Fibrous bands divided the tumour into lobules, in which the cells were mainly polygonal and arranged in sheets or trabeculae. The cells were relatively uniform in appearance with slightly basophilic cytoplasm. The nuclei contained prominent acidophilic nucleoli, which were often multiple. Mitotic activity was readily apparent with abnormal mitoses (Fig. 3). Nuclear pleomorphism was not marked, but several giant cells containing over 20 tightly packed nuclei were observed.

The specimen from the second operation showed several local recurrent tumour nodules up to 0.5 cm in diameter. In addition, a metastasis, 1 cm in length, was present in an oesophageal vein 8 cm below the site of the primary.

The left lower parathyroid was removed together with the carcinoma at the first operation, and the two right parathyroids were removed at the second operation. The left and right lower glands were of normal size, and they were not considered to be hyperplastic (Fig. 4). In contrast to this, the right upper gland was enlarged to 1 by 0.5 by 0.5 cm and consisted of chief cells with virtually no fat cells (Fig. 5). There was no nodule formation or rim, and no features of malignancy were present. This gland was hyperplastic in the face of severe hypercalcaemia.

CASE A2 (brother of the proband)

When 35 years old he presented at another hospital complaining of breathlessness and was found to have hypertension, nephrocalcinosis, and hypercalcaemia. An enlarged right lower parathyroid gland was subsequently removed and no other glands were located. After operation the serum calcium fell to normal and was still normal when he was seen four years later.

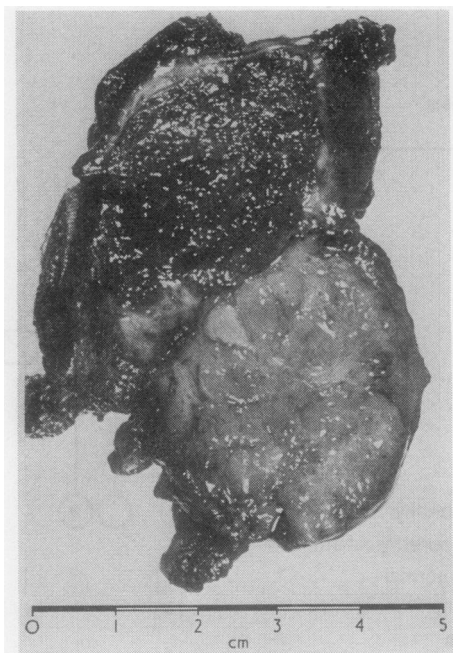


Fig. 2 Case A1. Resected left lobe of thyroid with parathyroid tumour invading posterior surface.

Pathology

The tumour weighed 2.8 g and was surrounded by a dense fibrous capsule. The gland parenchyma was penetrated by several fibrous bands, some of which were associated with iron pigment indicating previous haemorrhage. For the most part the gland consisted of chief cells with moderate nuclear pleomorphism and no mitotic figures. Although no rim of normal parathyroid tissue was seen, these appearances were consistent with the diagnosis of a parathyroid adenoma. However, in one area, the cells were larger, with more oxyphilic cytoplasm, prominent nucleoli, and a marked degree of mitotic activity—up to two per high-power field. These cells were polygonal or columnar with a tendency to form palisades around blood vessels but were not sharply demarcated from the surrounding parathyroid tumour cells. No vascular or capsular invasion was seen. This area was considered to represent possible malignant change in an adenoma.

CASE A3 (cousin of the propositus)

When 23 years old he presented at another hospital with cystitis and a bladder calculus. His serum calcium was measured several times and found to be between 2.88 and 3.30 mmol/l (11.5 and 13.2 mg/100 ml). Fifteen years later he is apparently well but the

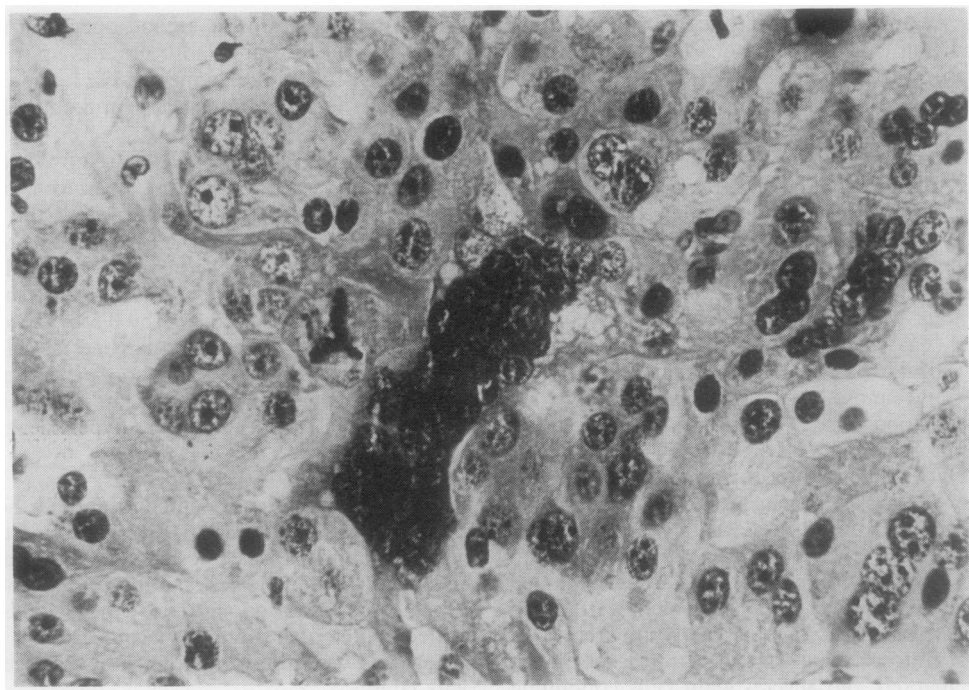


Fig. 3 Case A1. Parathyroid carcinoma with prominent nucleoli, an abnormal mitotic figure, and a multinucleate tumour cell (Haematoxylin and eosin $\times 445$).

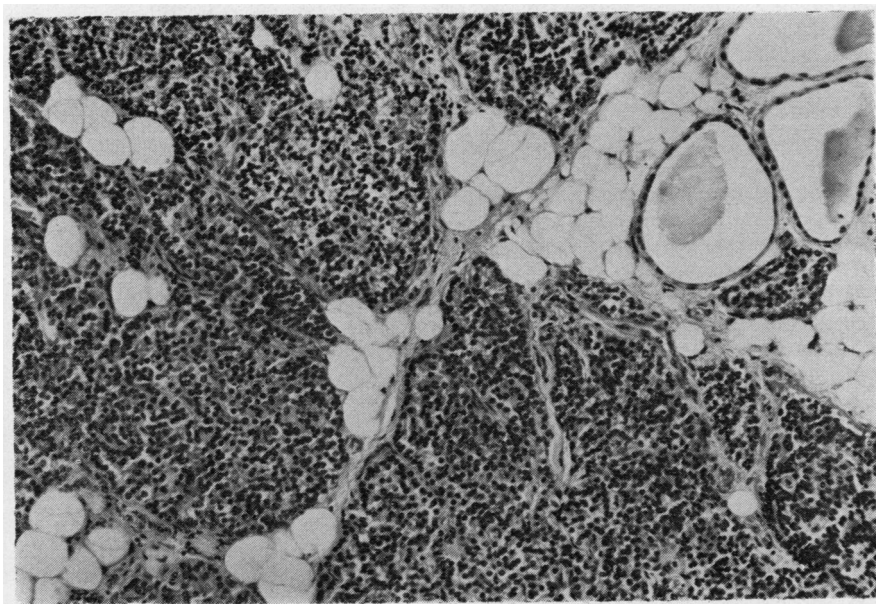


Fig. 4 *Case A1. Left lower parathyroid showing the presence of fat (H and E $\times 115$).*

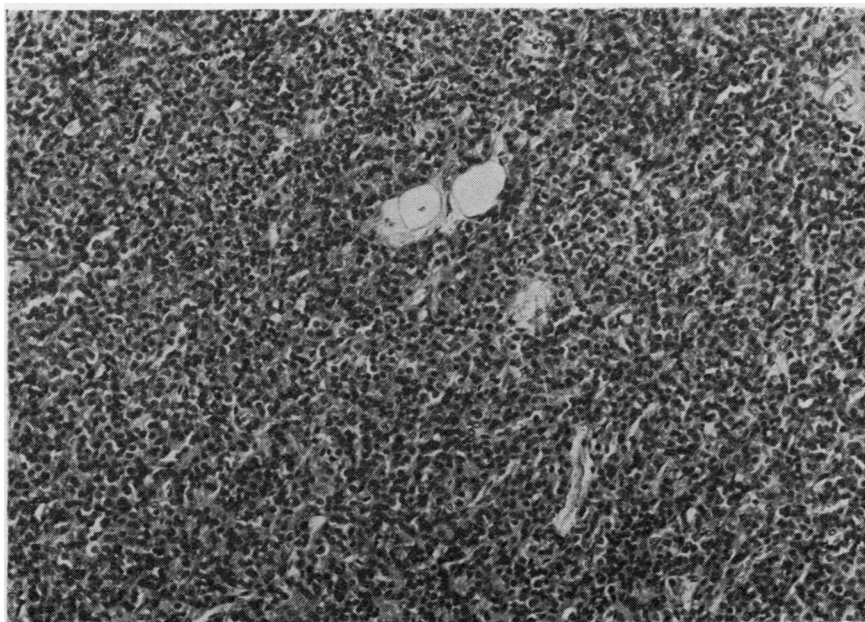


Fig. 5 *Case A1. Right upper parathyroid showing uniform sheets of chief cells with virtually no fat cells, in contrast to the left lower gland (Fig. 4) (H and E $\times 115$).*

serum calcium is at the upper limit of normal (2.63 mmol/l; 10.5 mg/100 ml) and further investigations are being carried out.

CASE A4 (uncle of the propositus)

He had suffered from dyspepsia since the age of 15 and at the age of 24 he had a gastroenterostomy for a pyloric ulcer. Two years later he had an operation for 'dental cysts'. The dyspepsia persisted but at the age of 30 a gastric test meal showed normal acid levels. After this a partial gastrectomy was performed. Four years later he developed renal failure due to nephrocalcinosis. He sustained pathological fractures of a clavicle and a rib and his serum calcium was 4.00 mmol/l (16.0 mg/100 ml). At operation a retrosternal parathyroid tumour was found and removed. He died of renal failure two years later at the age of 38.

Pathology

The gland was 1.8 cm in diameter and was encapsulated. The cells were mostly chief or vacuolated chief cells and fat was absent. The parenchyma was mainly arranged in trabeculae separated by a fine fibrous framework. There were neither large fibrous bands nor evidence of capsular or vascular invasion. The nuclei showed slight pleomorphism, nucleoli were not prominent, and only very occasional mitotic figures were seen. No rim of normal para-

thyroid was demonstrated and no other gland was available for examination. The tumour was considered to be a parathyroid adenoma.

CASE 5 (uncle of the propositus)

He developed a jaw tumour in his early 'teens after which his 'bones turned to chalk'. He was admitted to two hospitals during the 1920s but unfortunately no records survive. He died from this illness, which was almost certainly hyperparathyroidism, at the age of 14.

The daughter and mother of the propositus and one aunt are normocalcaemic but it has not so far proved possible to test the other members of this family. There is no clinical indication of parathyroid or other endocrine disorder in any other family member.

Family B (Fig. 6)

CASE B1

The propositus developed a swelling of the right molar region of the mandible at the age of 18, and radiological examination showed a rounded radio-lucent area. Serum calcium, phosphate, and alkaline phosphatase were normal. At operation a firm, gritty mass enucleated cleanly from a bony cavity. The lesion recurred eight years later and was again

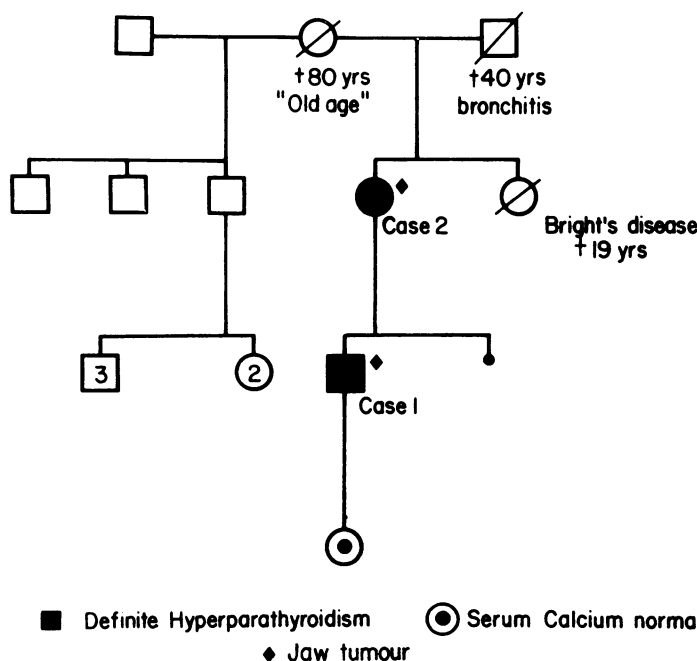


Fig. 6 Family tree of family B.

resected. At the age of 32 he presented with a two-year history of weakness, generalised aches and pains, dyspepsia, polydipsia, and polyuria.

On admission there were no abnormal physical findings, but laboratory investigations revealed hypercalcaemia (4.10 mmol/l; 16.4 mg/100 ml), hypophosphataemia (0.45 mmol/l; 1.4 mg/100 ml), raised serum alkaline phosphatase (125 iu/l), and a raised serum PTH (5 ng/ml). The blood urea was normal (3.5 mmol/l; 21 mg/100 ml). Radiological examination showed minimal subperiosteal erosions of the phalanges and small bilateral renal calculi. A barium swallow showed indentation of the oesophagus from the right. Surgical exploration revealed a large, hard, right-sided parathyroid tumour adherent to surrounding structures, including the oesophagus and the thyroid cartilage. Metastases were not seen and the other glands were not identified. The tumour was removed together with a small portion of the oesophageal wall, and after the operation the serum calcium and parathyroid hormone fell to normal.

Nine months after the operation the serum calcium had risen to 2.70 mmol/l (10.8 mg/100 ml) but the serum parathyroid hormone was only 0.4 ng/ml. However, five months later, while the serum calcium was 2.63 mmol/l (10.5 mg/100 ml) the serum PTH was 2.0 ng/ml, indicating a recurrence of hyperparathyroidism.

Pathology

The parathyroid tumour measured 3 by 2 by 2 cm. It was surrounded by a fibrous capsule and was divided by fibrous bands. The parenchyma was arranged in sheets with a few cribriform areas; there was no fat present. In one of the bands permeation of a small nerve by tumour cells was seen (Fig. 7), and there was possible capsular invasion. The tumour cells had pale granular cytoplasm, but some were oxyphilic, and a few had the appearance of small chief cells. There was a moderate degree of nuclear pleomorphism. Some cells had prominent acidophilic nucleoli and mitoses were present, although rare. The tumour was considered to be a parathyroid carcinoma.

The histological sections from the previous jaw lesions were reviewed. The two lesions were similar and each consisted of a whorled mass of densely cellular fibrous tissue with scattered acellular calcified foci (Fig. 8) and a small area of woven bone. The lesion had a sharply demarcated border with a capsule of loose fibrous tissue. No iron deposition, cyst formation or osteoclasts were seen. The features were considered to be those of an ossifying fibroma rather than osteitis fibrosa cystica.

CASE B2 (mother of the proband)

When the patient was aged 30 an osteolytic jaw tumour was resected. Seven years later a single

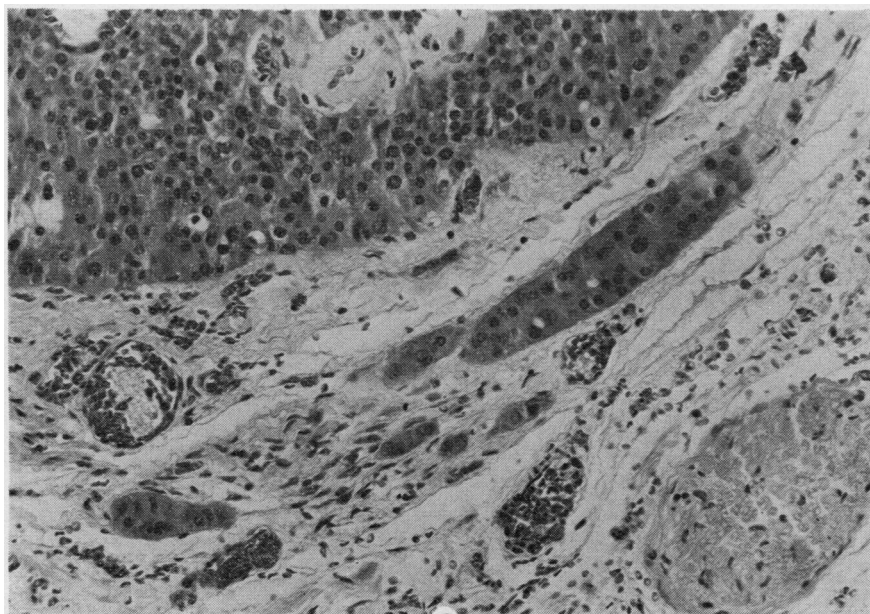


Fig. 7 Case B1.
Parathyroid carcinoma
showing invasion of a
nerve in fibrous tissue
(H and E $\times 155$).

enlarged parathyroid gland was removed. Clinical and biochemical details cannot be traced, but histological sections of the parathyroid tumour were recovered. She has had no recurrence of her symptoms of hyperparathyroidism in the 20 years since parathyroidectomy but refuses further investigation.

Pathology

The gland measured 1.2 by 0.7 cm and had a thick fibrous capsule. In the centre there was a collection of cholesterol clefts and acellular debris surrounded by a fibrous wall (Fig. 9). From this central area several fibrous bands radiated and there was iron deposition in the stroma and parenchyma, probably resulting from previous haemorrhage. The parenchyma consisted mainly of chief cells with a nodule of oxyphil cells. There was moderate nuclear pleomorphism and the nucleoli were not prominent. Neither mitoses nor capsular invasion were seen. The tumour was considered to be a parathyroid adenoma.

Discussion

These two families, together with the families described by Frayha *et al.* (1972), Mallette *et al.* (1974), and Leborgne *et al.* (1975), demonstrate that the parathyroid lesion in familial hyperparathyroidism can be malignant. In case A1 the tumour behaved in a highly malignant fashion with local recurrence and persistent severe hypercalcaemia, presumably due to more distant spread.

The tumour of her brother, case A2, showed some of the features of parathyroid carcinoma, namely, an area with marked mitotic activity, prominent nucleoli, and fibrous bands, only some of which were associated with haemorrhage. Schantz and Castleman (1973) described five features which may distinguish a parathyroid carcinoma from an adenoma—mitoses, trabecular arrangement of tumour cells, fibrous bands (but not if associated with haemorrhage), and vascular and capsular invasion. However, other authors have described mitotic activity in lesions which they considered to be benign (Norris, 1947; Smith, 1970). The presence of one or more prominent nucleoli in tumour cells is said to be suggestive of malignancy (Norris, 1948; Altenähr and Saeger, 1973). We consider that the appearance of the tumour in case A2 is not diagnostic of malignancy but suggests malignant transformation occurring in an adenoma. This appearance in the brother of a patient with parathyroid carcinoma, together with the finding of parathyroid carcinoma in two siblings (by both Frayha, *et al.* (1972) and Leborgne *et al.* (1975)), suggests that the parathyroid lesions in some families are unusually prone to malignant change.

The commonest parathyroid lesion in familial hyperparathyroidism and the MEN syndrome has been reported to be chief cell or nodular hyperplasia (Wermer, 1963; Cutler *et al.*, 1964). A number of families have also been described in which some or all members have had single parathyroid adenomas (Schachner *et al.*, 1966; Stevens *et al.*, 1967; Jackson and Boonstra, 1967). However, the distinction

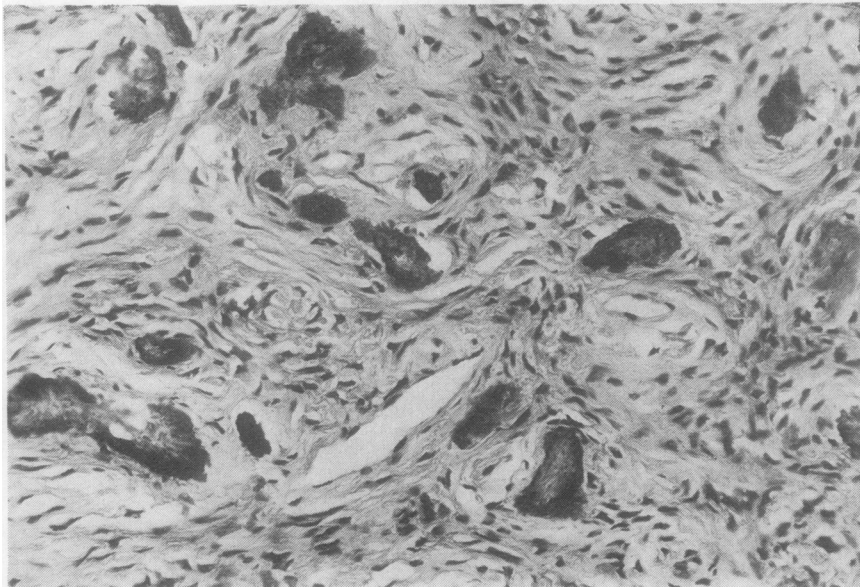


Fig. 8 Case B1.
Ossifying fibroma of the
jaw showing foci of
calcification (H and E
× 190).

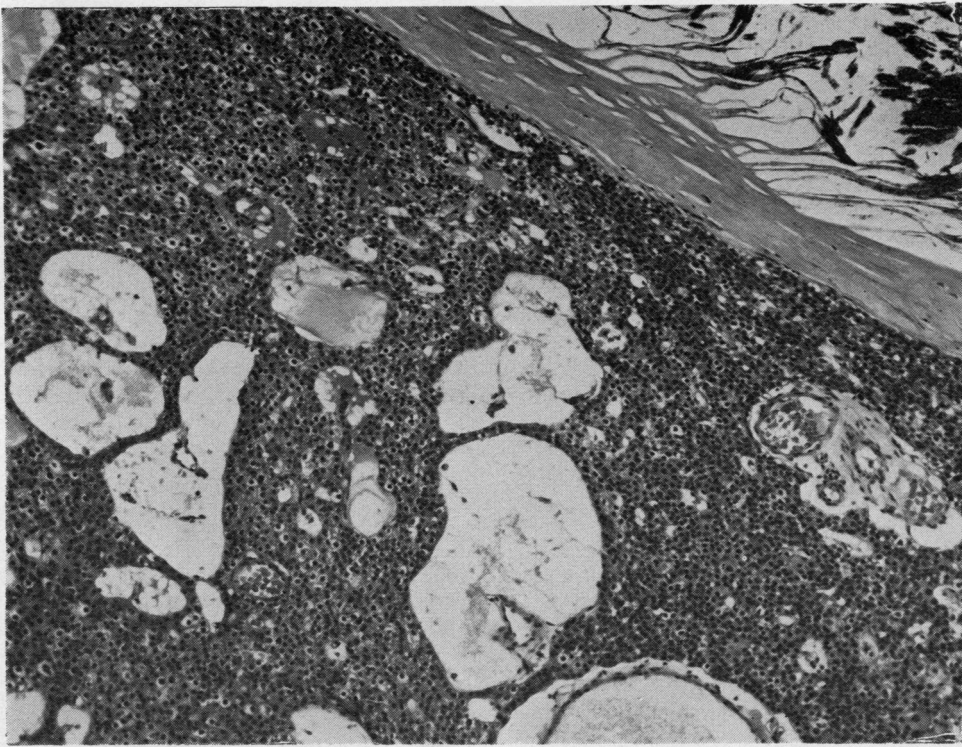


Fig. 9 Case B2. Parathyroid adenoma showing the edge of a nodule consisting of acellular debris surrounded by a fibrous capsule (H and E $\times 90$).

between adenoma and chief cell hyperplasia can be difficult. Indeed, Goldsmith *et al.* (1976) questioned whether the parathyroid lesions in the MEN syndrome are tumours at all. The development of a metastasis in case A1 of the present series proves that true tumours do occur in familial hyperparathyroidism.

The occurrence of both tumours and hyperplasia in familial parathyroid disease may be due to a progression from generalised parathyroid hyperplasia to formation of a tumour with, eventually, suppression of the other glands. A comparable sequence has been suggested in hyperparathyroidism secondary to renal failure (Roth quoted in Massachusetts General Hospital (1963) Case Records; Williams, 1974). The nature of the initial stimulus for the development of primary hyperplasia is unknown. Primary hyperplasia does not always affect all glands uniformly, and commonly affects the upper glands more than the lower (Cope *et al.*, 1958). In case A1 the extreme hypercalcaemia induced by the carcinoma may have suppressed the lower glands particularly. Only one gland was examined in case

B1, and the recurrent hyperparathyroidism may be due to metastatic carcinoma or hyperplasia of his other glands. In cases B2, A2, and A4, there was no recurrence of hyperparathyroidism in 20, 4 and 2 years after the removal of single glands, making hyperplasia unlikely. It is interesting that the case reported by Mallette *et al.* (1974) had two hyperplastic glands in addition to the carcinoma, and the two cases described by Frayha *et al.* (1972) each had an adenoma and a carcinoma. Either benign or malignant parathyroid tumours have also been reported in association with hyperplasia in non-familial primary hyperparathyroidism (Golden *et al.*, 1965; Kramer, 1970).

Familial hyperparathyroidism may occur alone or as part of the multiple endocrine neoplasia syndromes types I (Wermer, 1954) and II (Steiner *et al.*, 1968). Most reports suggest autosomal dominant inheritance of variable penetrance. The familial cases described here are compatible with that pattern of inheritance. In family A, a number of individuals both with and without hyperparathyroidism had peptic ulcers, but in the only individual

in whom gastric acid levels were measured they were normal, making Zollinger-Ellison syndrome unlikely. The only other endocrine abnormality was the occurrence of thyroid colloid nodules in some individuals in family A who did not have hyperparathyroidism, but this is not regarded as a feature of the MEN syndromes.

A number of non-endocrine conditions have been described in association with familial hyperparathyroidism and the MEN syndromes—fibrous dysplasia of bone and familial or non-familial hyperparathyroidism (Benedict, 1962; Firat and Stutzman, 1968); multiple lipomata and MEN I (Marshall and Sloper, 1954; Wermer, 1963); and multiple mucosal neuromas and MEN II (Williams and Pollock, 1966). In our family A, there were three individuals with ichthyosis including one case with hyperparathyroidism and one probable carrier of the gene. This association does not appear to have been described and may be a chance finding of two inherited conditions in one family.

The jaw lesions described in hyperparathyroidism are brown tumours (Jaffe, 1972) and fibrous dysplasia (Firat and Stutzman, 1968; Ehrig and Wilson, 1972). In family B, both members with hyperparathyroidism developed jaw tumours many years before the occurrence of hyperparathyroidism. At the time when the jaw tumour was removed from case B1 his serum calcium, phosphate, and alkaline phosphatase were all normal. This lesion was radiologically and surgically well demarcated and did not resemble fibrous dysplasia. Neither the characteristic bone trabeculae of fibrous dysplasia nor the iron-deposition and giant cells of a brown tumour were present. We feel that this lesion was an ossifying fibroma (Pindborg and Kramer, 1971). Kennett and Pollick (1971) described jaw tumours removed from a brother and sister 4 months and 18 months after resection of parathyroid adenomas. The histological description and illustration of the jaw lesions resemble those of our case B1. They concluded that the lesions were incompletely resolved brown tumours, without iron or giant cells, but we feel that they too could have been ossifying fibromas. This unusual jaw tumour may well be genetically linked to hyperparathyroidism rather than an atypical manifestation of parathyroid bone disease.

The study of these two families confirms the previous reports that parathyroid carcinoma can occur in familial hyperparathyroidism. It is not clear whether this is a chance occurrence, a generalised tendency in familial disease or a predilection of certain families. The occurrence of both a definite carcinoma and a possible malignancy in family A, together with the two reports of parathyroid carcinoma in siblings, suggests that the latter is the case

but elucidation of this point awaits further reports of the occurrence of this unusual parathyroid lesion in a familial setting.

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